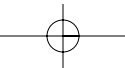
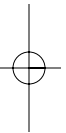
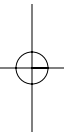
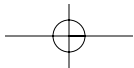
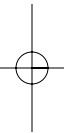
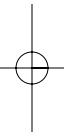
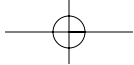


Part V

**Cancer Metastatic
to the
Central Nervous System**





Intracranial Metastases

W.K. ALFRED YUNG, LARA J. KUNSCHNER, RAYMOND SAWAYA, ERIC L. CHANG,
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Tumors that metastasize to the brain and intracranial space are very common, occurring in approximately 10% to 15% of patients with systemic cancers (Posner and Chernik, 1978; Cairncross and Posner, 1983; Walker et al., 1985). In contrast to the 17,500 new primary brain tumors that are expected to occur annually, more than 150,000 new cases of metastatic brain tumors occur each year in the United States (Posner, 1992). Moreover, the occurrence of metastasis to the brain is increasing as cancer patients live longer because of improved treatment and because the incidences of lung cancer and malignant melanoma continue to rise (Galicich et al., 1980a). The following are systemic cancers with a high incidence of metastasis to the brain

- Lung carcinoma
- Breast carcinoma
- Malignant melanoma
- Renal cell carcinoma
- Colorectal carcinoma

Lung carcinoma, especially small cell carcinoma and adenocarcinoma, is the most common type of cancer to metastasize to the brain, often with no evidence of systemic relapse (Figlin et al., 1988). The increase in the number of women and teenagers who smoke cigarettes and the increased rate of cigarette consumption has undoubtedly accounted for the increased number of young patients developing lung carcinoma and subsequent metastases to the brain.

Approximately 50% of patients with tumors metastatic to the brain present with single lesions, whereas the other 50% have two or more lesions (Delattre et al., 1988). A significant number of patients are found to have asymptomatic metastasis to the brain at the time of presentation with lung carcinoma (Salbeck et al., 1990).

Breast cancer is the second most common type of cancer to metastasize to the brain, occurring in approximately 10% of patients with advanced breast cancer (DiStefano et al., 1979). Some studies report that as many as 30% of patients experience concurrent systemic metastasis involving other organs, including the lung, bone, and liver (Tsukada et al., 1983). Younger patients and premenopausal patients are more prone to develop metastasis to the brain than are older, postmenopausal patients.

Malignant melanoma represents the third most common type of cancer having a high incidence of metastasis to the brain. An estimated 30% to 40% of patients with malignant melanoma will develop intracranial disease, including parenchymal and meningeal metastases (Byrne et al., 1983). In the brain, melanoma metastases are often hemorrhagic and multiple. The increasing incidence of melanoma metastasis to the brain may be the result of better control of extracranial disease through aggressive chemotherapy and biologic therapies.

Renal cell carcinoma and colorectal carcinoma are the fourth and fifth most common sources of brain metastases, respectively. Renal cell metastases, like

melanoma metastases, tend to be highly vascular and prone to hemorrhage. They produce single lesions more frequently than do lung cancer and melanoma and exhibit a rare, but well-documented, potential for producing late brain metastases that sometimes present more than a decade after resection of the primary renal tumor (Radley et al., 1993). The brain is one of the least frequent sites of metastasis from colorectal carcinoma; these metastases occur in approximately 5% of patients (compared with approximately 30% to 40% of melanoma patients, 35% of lung carcinoma patients, and 10% to 30% of breast carcinoma patients) (Cascino et al., 1983). Among patients who have solitary colorectal carcinoma metastases to the brain, it has also been shown that a disproportionately large percentage (approximately 50%) of metastases occur in the posterior fossa (cerebellar) (Dellatre et al., 1988).

These five types of metastatic tumors account for approximately 85% of all metastases to the brain (Dellatre et al., 1988). A large number of other systemic neoplasms may produce central nervous system (CNS) metastases, including hematologic malignancies (leukemia, lymphoma), a wide spectrum of systemic carcinomas, and, in small numbers but with increasing frequency, some varieties of sarcoma (Lewis, 1988).

PATHOLOGY

Intracranial metastatic disease may involve any of the three principal morphologic compartments: the dura, leptomeninges (subarachnoid space), or brain parenchyma. Metastases that initially involve only one compartment frequently invade other compartments as they grow. This is particularly true of parenchymal lesions located either very superficially in the gray matter or subjacent to the ventricular system. These lesions may secondarily breach the pia or ependyma, which allows them access to the ventricular system or subarachnoid space, and subsequently to disseminate widely via the cerebrospinal fluid pathways. Alternatively, tumors located primarily in the subarachnoid space (leptomeningeal carcinomatosis) often track centrally via the perivascular Virchow-Robin spaces (Fig. 13-1), with ultimate expansion into the brain parenchyma.

By far, the most commonly encountered site of metastasis from carcinoma and sarcoma is within the brain parenchyma. In contrast, metastasis resulting from leukemia preferentially involves the leptomeninges. Breast carcinoma tends to produce isolated dural metastases (Fig. 13-2) in addition to parenchymal lesions. Prostate carcinoma more commonly metastasizes to the skull and vertebrae than to

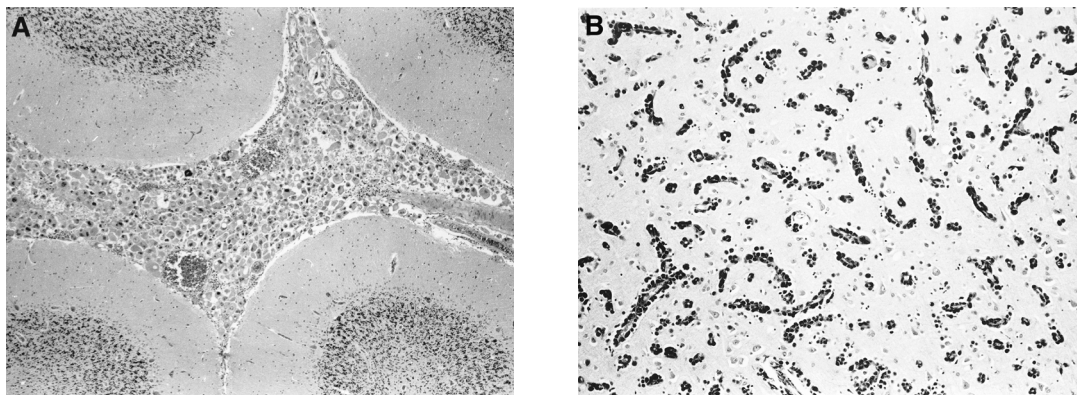


Figure 13-1. Leptomeningeal dissemination of tumor with secondary spread into brain parenchyma along perivascular (Virchow-Robin) spaces. (A) Melanoma cells fill the subarachnoid space. Once access to this strategic compartment has been gained, metastatic tumors can rapidly disseminate throughout the cerebrospinal fluid pathways of the neuraxis and may secondarily involve various anatomic constituents of the subarachnoid space such as blood vessels and cranial nerve rootlets or (B) may spread into the brain substance along the perivascular spaces of penetrating blood vessels. This is a common pattern of dissemination for melanoma and can also be seen with breast and other metastatic carcinomas. Diffuse leptomeningeal involvement is also frequently seen with the leukemias.

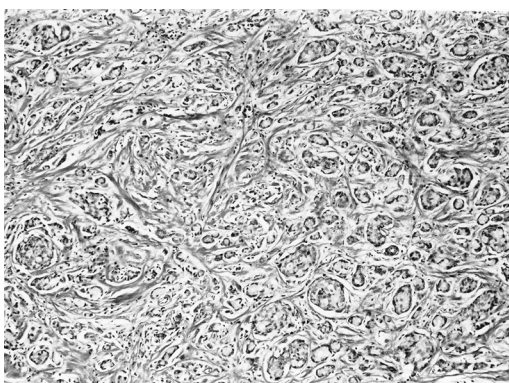


Figure 13-2. Dural metastasis. Breast carcinoma has a recognized tendency to produce dural metastases, as noted in this case in which cords and nests of infiltrating tumor cells are seen dissecting through the dense connective tissue of the dura. Such metastases from breast, prostate, lung, or other carcinomas can on occasion produce dural-based masses that mimic meningioma on neuroimaging studies.

the brain parenchyma, although intra-axial lesions may also occur. As in other locations, prostatic metastases to bone may be osteoblastic; in the cranium, such lesions may stimulate meningioma with hyperostosis.

Although parenchymal lesions may occur in any region of the CNS, several generalizations can be made:

1. Most metastases to the brain are supratentorial, the most common location being the cerebral hemispheres, where tumor emboli tend to lodge in the vascular gray matter, particularly at the gray matter–white matter interface where penetrating vessels narrow in caliber (Fig. 13-3).
2. Cortical hemispheric metastases are most frequently found in the vascular distribution territory of the middle cerebral arteries, particularly in the arterial border zones.
3. Metastases also occur frequently in the deep cerebral gray nuclei and white matter, as well as in the cerebellum.
4. Brain stem and spinal cord lesions occur far less frequently, but metastases may involve virtually any anatomic locus within the CNS, including such specialized organs as the choroid plexus, pineal gland, and pituitary.

In rare cases, systemic neoplasms may metastasize to a pre-existing primary brain tumor. The vast ma-

jority of such cases involve metastasis of a primary lung or breast carcinoma to a meningioma; very rarely, the host tumor is a schwannoma or glioma (Schmitt, 1984).

Microscopic Features

Intraparenchymal metastases tend to expand as roughly spherical masses and establish a well-defined interface with the surrounding brain parenchyma (Fig. 13-4). This sharp circumscription stands in contradistinction to the diffusely infiltrating margins of most primary brain tumors and can be of considerable practical importance to the surgical patholo-

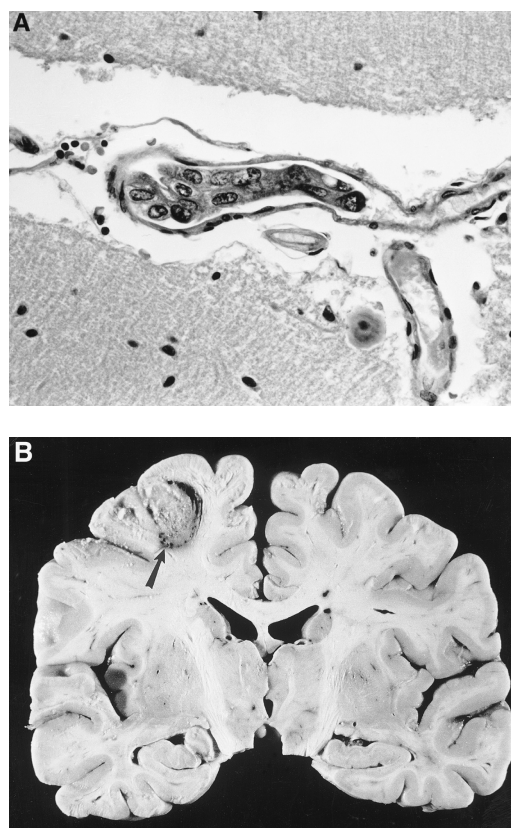


Figure 13-3. Parenchymal metastasis. (A) Most metastases originate by hematogenous dissemination of tumor emboli. (B) As illustrated in this case of metastatic lung adenocarcinoma, parenchymal metastases are commonly supratentorial, cortical in location, centered around the gray–white junction, and most frequently lie in the vascular distribution territory of the middle cerebral artery, particularly in the parasagittal arterial boundary zones.

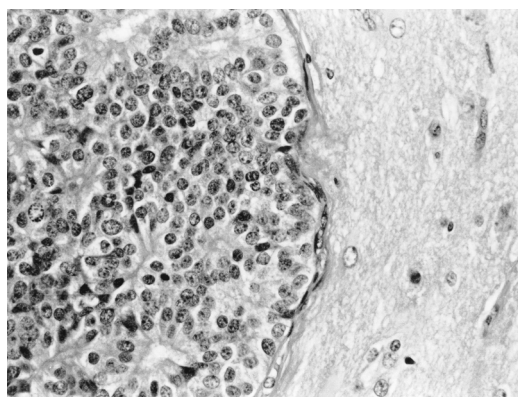


Figure 13-4. Interface of metastatic tumor with brain parenchyma. Sharp macroscopic (as in Fig. 13-3B) and microscopic circumscription is the rule for most metastatic tumors; for the surgical pathologist this is a useful diagnostic feature, and for the neurosurgeon it often permits total excision of the neoplasm. A notable exception to this rule is metastatic lymphoma, which, like primary CNS lymphoma, diffusely infiltrates nervous tissue from angiocentric foci.

gist, especially when dealing with small biopsy specimens of tumors that occur in the absence of a known primary systemic neoplasm.

As discussed, the overwhelming majority of tumors that give rise to CNS metastases are carcinomas; however, a variety of sarcomas may also metastasize to the CNS (Lewis, 1988). For all types of tumors, the morphology of the metastatic lesion in many cases recapitulates that of the primary neoplasm with great fidelity (Fig. 13-5). The degree of differentiation exhibited ranges from the metastatic lesion being almost pathognomonic of the primary organ of origin to being so poorly differentiated that only a diagnosis of metastatic carcinoma or metastatic malignant neoplasm can be made based on morphologic criteria. The brain parenchyma surrounding most metastatic lesions typically exhibits a robust reactive astrogliosis, a fact that must be considered when interpreting needle biopsy specimens obtained from this vicinity.

Immunostaining may be helpful in the diagnosis of some cases, particularly in distinguishing metastatic carcinoma from the other two major types of malignant neoplasms that involve the CNS parenchyma of older individuals: glioblastoma and primary CNS lym-

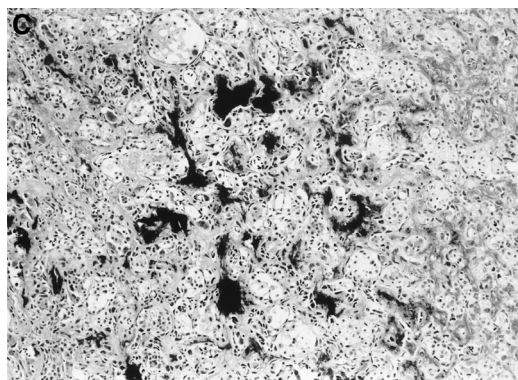
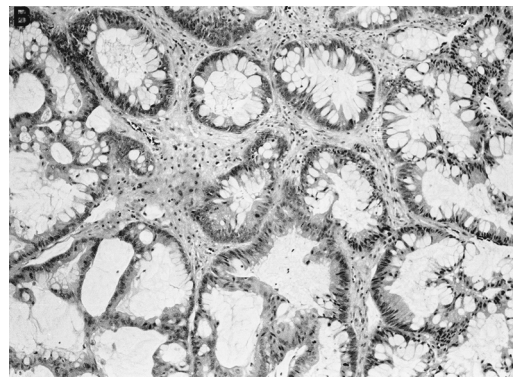
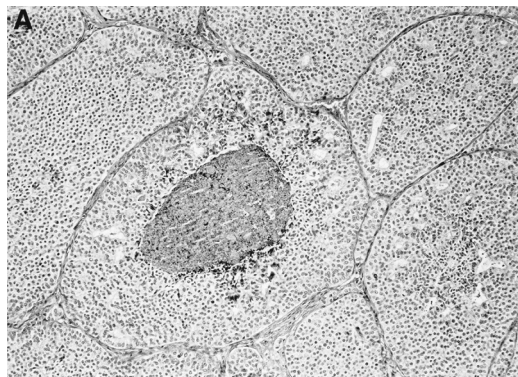


Figure 13-5. Histology of metastases. Many metastatic tumors closely recapitulate the morphology of the primary neoplasm, as illustrated here with (A) metastatic breast carcinoma, (B) mucinous colon carcinoma, and (C) osteosarcoma. Frequently, however, metastases are poorly differentiated and lack suggestive histologic features. Often, in the clinical setting of an unknown primary tumor, only a diagnosis of metastatic carcinoma or adenocarcinoma can be rendered in such cases, along with a list of the most likely primary sites.

phoma. In small and/or poorly preserved biopsy specimens, all three of these tumor types may appear quite similar on hematoxylin and eosin (H&E)—stained tissue sections: they are all high-grade pleomorphic tumors that show large atypical tumor cells, mitotic figures, and tumor necrosis. The basic panel of immunostains typically used in this situation is (1) glial fibrillary acidic protein (GFAP), which is positive only in gliomas; (2) a mixture of low- and high-molecular-weight keratin antibodies (“keratin cocktail”) for metastatic carcinoma; and (3) the lymphoma markers CD45 (leukocyte common antigen), CD3 (a T-cell marker), and CD20cy (L26, a B-cell marker), either separately or combined as a “CNS lymphoma cocktail.” This panel will usually permit separation of the three tumor types and definitive identification of metastatic carcinoma when present.

One important caveat is that many glioblastomas will show cross-reactivity with keratin antibodies; however, the GFAP immunostain will only be positive in glioblastomas, not in carcinomas or lymphoma. Once a diagnosis of metastatic carcinoma has been made, it is sometimes, but not always, possible to confirm the primary site of origin. If the patient has a known primary, a tentative diagnosis of metastatic carcinoma consistent with the primary can be rendered and immunostaining may not be necessary. If there is no known primary, a thorough clinical evaluation of the patient is required. For metastatic carcinomas in patients in whom no primary site can be identified after clinical work-up, a number of antibodies can be used to help identify tumor-specific phenotypic features. Unfortunately, many of the antibodies currently used in immunopathology are not uniformly as specific as one would like, and, therefore, both positive and negative antibody immunostaining must be interpreted with caution and in the context of the patient’s clinical history. Nevertheless, antibody studies can be helpful. Useful antibodies include estrogen and progesterone receptor antibodies for breast carcinoma; thyroid transcription factor 1 (TTF-1) for lung and thyroid carcinomas; prostatic acid phosphatase (PAP) and prostate-specific antigen (PSA) for prostate carcinoma; and thyroglobulin (as well as TTF-1) for thyroid carcinoma. Again, it must be stressed that all these antibodies may show positivity in other carcinomas, and the results should not be considered absolute.

Another approach that has been taken is the use of several keratin antibodies of differing molecular weight together with other markers in large panels;

diagnostic algorithms are then used to give estimates of the most likely primary site(s) based on the particular pattern of reactivity seen. Again, as with the use of individual antibodies, panel results can be helpful in directing attention to primary sites that should be investigated further clinically, but findings should be interpreted with caution. Brief mention must also be made of metastatic melanoma. Heavily pigmented lesions are easy to diagnose; however, up to a one-third of brain metastases appear amelanotic on H&E-stained slides, and melanoma may initially present as a CNS metastasis from an unknown primary tumor. Immunomarkers usually employed in this situation are S-100 protein, HMB-45, and MART-1.

PATHOPHYSIOLOGY

It is generally accepted that most metastatic brain tumors arise as a result of the hematogenous spread of cancer cells to the brain. Because brain microvessels are structured differently from systemic microvessels, cells destined to metastasize to the brain first adhere to and then penetrate the blood–brain barrier (BBB) formed by endothelial cells. Cells must penetrate the basement membrane and astrocytic foot processes before reaching the “soil” that allows their proliferation in brain parenchyma (Nicolson, 1982).

This process is thought to be nonrandom, as proposed by the “seeds” and “soil” hypothesis for cancer metastasis (Paget, 1989). The properties of the tumor cells, or “seeds,” that determine the preferential development of brain metastasis from certain types of cancer include the quantitative expression of specific adhesive molecules that allow preferential adhesion to brain endothelial cells (Nicolson, 1988a,b) and the increased production of certain degradative enzymes, such as type IV collagenase and heparinase, that may enable tumor cells to penetrate the endothelial junction and the basement membrane (Liotta et al., 1991). Once the metastatic cells have penetrated the BBB, they proliferate in the appropriate microenvironment, or “soil,” indigenous to brain parenchyma. Certainly, locally produced growth factors may stimulate the growth of specific metastatic tumor cells (Cavanaugh and Nicolson, 1991). In the brain, fibroblast growth factor, which has been found in high levels in the normal brain, may have such an effect (Rodeck et al., 1991).

Metastatic brain tumors, as opposed to primary malignant gliomas, usually grow as well-demarcated,

spherical masses that are often amenable to total excision by surgery. Another difference between metastatic tumors and primary malignant gliomas is that brain metastases generally grow more rapidly and exhibit a high bromodeoxyuridine labeling index, often in the range of 20% to 25%, indicating a large proliferating fraction of tumor cells (Cho et al., 1988). Most gliomas, on the other hand, have lower labeling indices. Metastatic tumors are solid or cystic as a result of central necrosis; some tumors, such as metastases from melanoma, choriocarcinoma, and testicular carcinoma, are often hemorrhagic and tend to invade the vascular wall (Pullar et al., 1985).

CLINICAL PRESENTATION

The clinical presentation of patients with metastases to the brain depends on the number and location of the metastases. Multiple metastases frequently occur in lung carcinoma, breast carcinoma, and malignant melanoma; single metastases more commonly occur in patients with colorectal and renal cell carcinoma (Delattre et al., 1988). The common presenting symptoms in patients with metastases to the brain are listed in Table 13-1. Most patients present with complaints secondary to an increase in intracranial pressure (headache, mental change, or somnolence) or with focal (complex partial) or generalized seizures.

Patients with a single metastasis usually develop focal symptoms and signs in addition to headache and change in mental status. These may include (1) cranial nerve palsies, usually involving nerves VI and VII; (2) dysphasia; (3) visual deficits; (4) hemiparesis; or (5) hemisensory loss. Patients with multiple brain

metastases can also present with diffuse, nonlocalized symptoms, such as generalized weakness and bowel and bladder incontinence. Surprisingly, many patients have few or no obvious symptoms and signs; thus, a physician should have a high index of suspicion for patients at risk of developing brain metastases.

IMAGING

The diagnosis of brain metastasis is confirmed with computed tomography (CT) or magnetic resonance imaging (MRI) when the patient's history and neurologic examination raise the possibility of this diagnosis. Magnetic resonance imaging with gadolinium contrast enhancement represents the most sensitive diagnostic tool used to detect the presence of single or multiple metastases. Cerebrospinal fluid examination is only helpful in the presence of meningeal metastasis.

The presence of a single lesion seen on a CT or MRI scan in a patient with progressive systemic cancer is not an unequivocal indication of brain metastasis. The possibility that the lesion may be a cerebral abscess, a malignant glioma, or a meningioma must be considered and carefully ruled out. This will often require surgical biopsy or, preferably, excision of the lesion.

In patients who present with neurologic symptoms and whose CT or MRI results show a contrast-enhancing mass suggestive of a metastatic lesion, the primary cancer must be located before the brain lesion can be treated. The most common primary site will be the lung in men and the lung or breast in women. Once a brain metastasis has been discovered, the recommended techniques for screening systemic tumors are anteroposterior and lateral chest radiographs, chest CT scan if chest radiograph results are negative, mammogram (in women), bone scan, urinalysis, and stool guaiac test for occult blood (Voorhies et al., 1980). If these tests fail to identify a primary tumor site, surgical resection of the cerebral lesion can often provide the pathologic diagnosis. Frequently, however, metastatic adenocarcinomas do not exhibit pathognomonic morphologic features, and only a diagnosis of metastatic adenocarcinoma can be rendered. Not surprisingly, in one recent study, 85% of adenocarcinomas of unknown origin were ultimately found to have originated in the lung (Mrak, 1993). If there is more than one lesion in the brain, the largest or the most symptomatic lesion should be chosen first for surgical resection.

Table 13-1. The Most Common Presenting Symptoms in Patients With Metastases to the Brain

<i>Symptoms</i>	<i>Relative Frequency at Diagnosis (%)</i>
Headache	71
Seizures	54
Mental change	52
Hemiparesis	43
Vomiting	32
Dysphasia	27
Impaired consciousness	25
Visual change	25

TREATMENT

General Considerations

The first stage of treatment for patients with single or multiple metastases to the brain is to stabilize acute neurologic symptoms caused by increased intracranial pressure and, in some patients, status epilepticus. Headache, nausea and vomiting, and change in mental status are the most common signs and symptoms of increased intracranial pressure. Patients with these symptoms should begin steroid treatment immediately (Cairncross and Posner, 1981). The typical starting bolus is 10 to 20 mg, followed by 16 mg/day in divided doses. The antiedema effect of steroids can often provide dramatic relief of symptoms such as headache and mental confusion. If the CT or MRI scan shows a marked increase in cerebral edema and evidence of impending herniation, the steroid dose can be increased to 24 or 30 mg/day with an initial loading dose as high as 100 mg, if necessary.

In patients showing signs of cerebral herniation, steroids usually do not take effect fast enough to reverse the rapid progression of neurologic dysfunction and impending death. Hyperventilation and intravenous hyperosmotic agents such as mannitol must be initiated immediately in addition to steroid therapy. Endotracheal intubation may be required to achieve adequate hyperventilation in obtunded or comatose patients. A $p\text{CO}_2$ level of 20 to 25 should be maintained to achieve optimal vasoconstriction. Mannitol should be given as a 20% solution at a dose of 1 to 2 g/kg body weight every 6 hours after an initial dose of 50 to 100 g administered intravenously over 20 to 30 minutes. The subsequent dose of mannitol can be adjusted according to the patient's level of consciousness and be tapered off when the patient's condition stabilizes with steroids (Ravussin et al., 1988).

Generalized or partial seizures are the presenting symptoms in 15% to 25% of patients with metastasis to the brain and are most common in patients with superficial lesions near the cortical gray matter. Status epilepticus can be lethal if allowed to continue for a prolonged period and should be eliminated with intravenous diazepam, lorazepam, or phenytoin, depending on the preference of the treating physician. Maintenance therapy should be initiated for long-term treatment. Phenytoin remains the most commonly used anticonvulsant, but carbamazepine and sodium

valproate should also be considered. Unfortunately, there has been no study to compare the efficacy of these three drugs in this group of patients. However, several studies have reported fluctuation of phenytoin levels in patients receiving systemic chemotherapy (Grossman et al., 1989). Thus, the necessary anticonvulsant level should be monitored more frequently to maintain adequate control of seizures. Moreover, the issue of prophylactic anticonvulsant therapy in patients with metastasis to the brain or a primary brain tumor without seizures as a presenting symptom has not been resolved (Cohen et al., 1988). Despite the use of prophylactic anticonvulsants, the incidence of seizures with a later onset is the same as in patients not receiving prophylactic anticonvulsants. Nevertheless, it is advisable to start the patient on an anticonvulsant if the lesion is located in an epileptogenic area.

Radiation Therapy

The benefit of administering external-beam radiation therapy to patients afflicted with metastatic deposits of cancer in the brain was first reported by Chao and colleagues (1954) and subsequently by Chu and Hilaris (1961). Since that time, intermediate-dose whole-brain irradiation delivered in daily fractionation over 1 to 4 weeks has been considered the standard therapeutic approach for such patients (Coia et al., 1988). In numerous prospective and retrospective series, the value of cranial irradiation in preventing or delaying progression of neurologic deficits, restoring function, and decreasing steroid dependency has been well documented (Order et al., 1968; Borgelt et al., 1980; West and Maor, 1980; Kurtz et al., 1981).

The Radiation Therapy Oncology Group (RTOG) conducted several large phase III randomized trials in the 1970s evaluating the efficacy of myriad cranial irradiation fractionation schedules that varied radiation fraction sizes, total radiation doses, and times of treatment. The first two studies evaluated five one-fraction-per-day fractionation schemes: (1) 20.0 Gy in five 4.0-Gy fractions over 1 week; (2) 30.0 Gy in 10 3.0-Gy fractions over 2 weeks; (3) 30.0 Gy in 15 2.0-Gy fractions over 3 weeks; (4) 40.0 Gy in 15 2.67-Gy fractions over 3 weeks; and (5) 40.0 Gy in 20 2.0-Gy fractions over 4 weeks (Borgelt et al., 1980). No differences in survival time (less than 26 weeks), time to neurologic progression (12 to 19 weeks), or frequency of neurologic improvement were observed among these treatment arms.

From 1976 to 1979, the RTOG evaluated two radiation schedules for 255 patients whose distant metastases were limited to the brain and whose primary tumor was controlled or absent. The patients were randomized to receive 30.0 Gy in 10 3.0-Gy fractions over 2 weeks or 50.0 Gy in 20 2.5-Gy fractions over 4 weeks (Kurtz et al., 1981). No differences in palliative results or survival were observed. As a result of reports from these studies, 30.0 Gy in 10 3.0-Gy fractions has become the most commonly administered radiation regimen in the United States for patients with brain metastases, although the use of more protracted fractionation schemes should be considered in certain instances and is discussed later.

Patient factors are important in the evaluation of treatment response and outcome in clinical trials. Diener-West and coworkers (1989) used multivariate analysis to identify favorable subgroups of patients for future protocols and showed that four factors were associated with improved survival: having a Karnofsky performance scale (KPS) score of 70 or more, having an absent or controlled primary tumor, being younger than 60 years old, and having metastatic disease limited to the brain. Patients with all four favorable characteristics had a predicted 200 day survival of 52%. Those with none of the favorable factors had a predicted survival of 1.8 months (Diener-West et al., 1989). These prognostic factors were again identified by recursive partitioning analysis of a database from three consecutive RTOG trials. Three classes of patients were proposed: Class 1 included patients with a KPS score of ≥ 70 who were < 65 years of age and who had a controlled primary tumor but no extracranial metastases; class 3 included those with a KPS score of < 70 ; class 2 included all remaining patients (Gaspar et al., 1997).

An RTOG phase I/II trial of accelerated fractionation in patients with brain metastases prescribed whole-brain radiation of 1.6 Gy twice daily separated by 4 to 8 hours delivered for 5 days a week to 48 to 70.4 Gy. Analysis of the results suggested that dose escalation was tolerated without excessive toxicity and might improve survival in patients receiving 54 Gy or greater (Sause et al., 1993). In the follow-up RTOG phase III study, 445 unresected patients were randomized to receive either accelerated hyperfractionation of 1.6 Gy b.i.d. to 54.4 Gy or accelerated fractionation of 30 Gy in 10 fractions. Unfortunately, this trial failed to demonstrate any improvement in survival with 54.4 Gy (Murray et al., 1997).

Radiation sensitizers such as misonidazole and bromodeoxyuridine have been investigated by the RTOG. Randomized studies of patients with brain metastases have failed to show any statistically significant survival benefit with the administration of either compound along with whole-brain radiation therapy (WBRT) (Komarnicky et al., 1991; Phillips et al., 1995). Motexafin gadolinium texaphyrin (XCYTRIN), a drug that comes from a family of ring-shaped molecules adapted from porphyrin molecules, is being investigated as a radiation sensitizer in the treatment of brain metastases. The results from the phase I and II studies found that it was well tolerated when administered daily with WBRT (Viala et al., 1999; Mehta et al., 2000). A randomized phase III trial has been initiated.

Patchell and coworkers (1990) demonstrated a survival advantage for selected patients with resectable, single brain metastases randomized to receive resection and cranial irradiation over patients given cranial radiation alone, and this trial established surgery and postoperative irradiation as the standard approach for such patients. The study was limited to patients with a KPS score of 70 or greater and confirmed the benefit of resecting solitary lesions that had been previously suggested in nonrandomized study reports (Galicich et al., 1980a; Sause et al., 1990). The postoperative cranial radiation was delivered in 12 3.0-Gy fractions to a total dose of 36.0 Gy.

Several retrospective studies have examined the role of postoperative radiation therapy for patients with brain metastases (Dosoretz et al., 1980; DeAngelis et al., 1989b; Hagen et al., 1990; Smalley et al., 1992; Armstrong et al., 1994; Skibber et al., 1996). The majority of these studies do not demonstrate a survival benefit from adding WBRT after surgery. A prospective randomized study by Patchell and coworkers (1998) is the only one that addresses this issue. Ninety-five patients with a single metastasis to the brain were treated with complete surgical resection and were then randomized either to treatment with postoperative WBRT or to observation. Recurrence of metastases in the brain was less frequent in the radiation group (18%) than in the observation group (70%) ($p < 0.001$). Postoperative radiotherapy prevented brain metastasis recurrence at both the site of the original lesion (10% versus 46% for the untreated group; $p < 0.001$) and at other sites in the brain (14% versus 37%, respectively; $p < 0.01$). Deaths from neurologic causes were also reduced by

administration of WBRT (14% versus 44% for untreated patients; $p = 0.003$). This reduction in neurologic deaths was seen only in those patients receiving WBRT immediately after surgery and not at the time of recurrence. No significant difference in overall survival was observed for untreated or irradiated patients. On the basis of randomized data demonstrating the reduction of neurologic deaths in patients receiving postoperative WBRT, it is reasonable to recommend its routine use.

Stereotactic radiosurgery was introduced in 1951 by the Swedish neurosurgeon Lars Leksell as a technique designed "to destroy" the target lesion with a single large dose of radiation delivered with a series of narrow radiation beams. Stereotactic radiation techniques exhibit rapid dose fall-off at the target edges, permitting significant sparing of normal brain tissue (Phillips et al., 1994). Numerous reports from different institutions support the use and effectiveness of radiosurgery for brain metastases (Wen and Loeffler, 1999). A multi-institutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastases showed that radiosurgery in conjunction with WBRT for a single brain metastasis can produce a substantial functional survival time of 56 weeks from the date of radiosurgery in patients with good performance status and who lack extracranial metastases. The comparability of these results to surgical series suggested that a randomized comparison of radiosurgery with surgery for brain metastasis treatment would be of great interest (Shaw, 1999). Such a trial is concurrently open to patients with a single brain metastasis at The University of Texas M. D. Anderson Cancer Center (M. D. Anderson). There are apparent advantages to either radiosurgery or surgery, depending on the clinical scenario. Surgery provides immediate resolution of mass effect and tissue for pathologic diagnosis if needed and poses no risk of radiation necrosis (Loeffler and Alexander, 1993). With radiosurgery, there are decreased risks of hemorrhage, infection, and tumor seeding as well as reduced costs produced, in part, by not requiring hospitalization.

The question has been raised by the results of the multi-institutional radiosurgery series as to whether radiosurgical treatment can improve survival beyond that produced by WBRT alone. This question was addressed by a study from the University of Pittsburgh in which 27 patients who had 2 to 4 metastases (<25 mm in diameter) were randomized to initial man-

agement with WBRT or with WBRT plus radiosurgery (Kondziolka et al., 1999). Local failure of tumor control was 100% in those receiving WBRT alone but was only 8% in those who received a radiosurgery boost. The median time to local failure was 6 months after WBRT alone and 36 months after WBRT plus radiosurgery ($p = 0.0005$). The median time to any local control failure in the brain was improved in the radiosurgery arm of the study (34 months) relative to the WBRT-alone arm (5 months; $p = 0.002$). Patients in the radiosurgery arm had a median survival time of 11 months versus 7.5 months in the WBRT-alone arm, but this difference was not statistically significant. The RTOG 95-08 trial, which is nearing completion, compares WBRT with or without a radiosurgery boost and stratifies patients as having a single metastasis or two to three metastases.

The role of WBRT after radiosurgery has been examined in a retrospective study by the group at the University of California at San Francisco, which reported on 106 patients with single or multiple brain metastases that were managed initially with radiosurgery or radiosurgery plus WBRT (Sneed et al., 1999). In the two treatment groups, both median survival and 1 year freedom from progression were similar at 11.3 months versus 11.1 months and 71% versus 79%, respectively. However, freedom from tumor progression in the brain at 1 year was significantly worse for the group treated by radiosurgery alone (28%) than for the group receiving radiosurgery plus WBRT (69%). The authors analyzed the results further by allowing for successful salvage of the first failure and found that if this was allowed, local control of tumor growth within the brain at 1 year was not significantly different for the two study arms (62% versus 73% at 1 year; $p = 0.56$) (Sneed et al., 1999). The group at the University of Heidelberg reported on a series of 311 brain metastases in 236 patients, each of whom had one to three brain metastases (Pirzkall et al., 1998). One hundred fifty-eight patients received radiosurgery only to a median dose of 20 Gy. The remaining 78 patients received a median radiosurgical dose of 15 Gy, followed by WBRT. Overall median survival time for patients was 5.5 months, and CNS disease control was achieved in 92% of treated brain metastases. Results were not significantly different for patients who did or did not receive WBRT, but there was a trend toward improved local control at 2 years (86% with WBRT versus 72% without it; $p = 0.13$). Interestingly, for patients without extracranial dis-

ease, there was a trend toward increased survival in patients receiving WBRT (15.4 months) relative to those not receiving it (8.3 months) ($p = 0.08$) (Pirzkall et al., 1998). The role of WBRT after radiosurgery warrants further study in a randomized trial that should include patient survival, freedom from progression, and a validated quality of life questionnaire component as endpoints to be evaluated.

Metastases from renal cell carcinoma and melanoma are described as "radioresistant" because of their lack of response to conventional radiotherapy. These histologic types deserve special attention and discussion. A review of the experience at M. D. Anderson with brain metastases from renal cell carcinoma described 119 patients who were treated with WBRT alone (Wronski et al., 1997). Overall median survival time of patients with the diagnosis of brain metastases was 4.4 months, and the cause of death was neurologic in 76% of patients and systemic in 16%. The authors suggest more aggressive approaches that include surgery or radiosurgery because of these unsatisfying results. A report from the University of Pittsburgh described the treatment of 35 patients who had 52 renal cell carcinoma metastases that were treated with radiosurgery over a 9 year period (Mori et al., 1998b). WBRT was given to 28 patients, and their median survival was 11 months after radiosurgical treatment. A 90% local control rate was achieved (21% disappearance, 44% tumor regression, 26% stable disease). The addition of WBRT did not improve survival or reduce distant failure (development of remote tumors) within the brain. However, local failure was only observed in the radiosurgery-alone arm of the study, leading the authors to hypothesize that WBRT might contribute to local control of tumor growth. The number of local control failures is small in this study, making it difficult to draw firm conclusions about the ability of WBRT to improve local control (Mori et al., 1998b).

The Harvard University group reported that melanoma and renal cell carcinoma metastases can be controlled just as easily with radiosurgery as tumors having "radiosensitive" histologies (Alexander et al., 1995). The University of California at San Francisco reported the use of gamma knife radiosurgery to treat brain metastases from melanoma in a series of 55 patients, including 16 treated for recurrence, 11 of whom received radiosurgery as a boost to WBRT, and 28 treated with radiosurgery alone as initial management (Seung et al., 1998). Median patient survival time was 35 weeks, and the only significant factor in

multivariate analysis of survival was target volume of the tumor. No significant difference was seen in actuarial freedom from development of intracranial progression by log-rank analysis ($p = 0.85$), comparing patients treated with radiosurgery alone, radiosurgery plus WBRT, or radiosurgery for recurrence. Thus, the role of WBRT and how best to integrate it with radiosurgery in the management of melanoma and renal cell carcinoma, remains to be defined.

A series of patients who had single brain metastases from melanoma was also reported from the University of Pittsburgh, and the authors concluded that radiosurgery alone was appropriate because WBRT did not improve survival or local tumor control. New brain metastases developed less frequently with the addition of WBRT, but this was not statistically significant (Mori et al., 1998a). A multi-institutional report of the use of radiosurgery for single brain metastases demonstrated that tumor control improved significantly for melanoma and renal cell carcinoma relative to other tumor types ($p = 0.0006$) (Flickinger et al., 1994). Radiosurgery is thus an apparently effective modality for treating the so-called "radioresistant" tumor histologies such as solitary brain metastases from renal cell carcinoma and melanoma.

The subject of re-irradiation often arises when patients who have already received WBRT develop new, persistent, or recurrent brain metastases. Loeffler and co-workers (1990) treated 18 patients who had 21 recurrent or persistent brain metastases with radiosurgery. Patient eligibility requirements for treatment were having a KPS score that was ≥ 70 and having stable systemic disease. With a reported median patient follow up of 9 months, all tumors in the radiosurgery field were controlled, and no cases of symptomatic radiation necrosis occurred despite previous radiation treatment (Loeffler et al., 1990). A study to determine the maximum tolerable dose of single-fraction radiosurgery in patients with previously irradiated primary brain tumors or brain metastases was carried out by the RTOG study 90-05 (Shaw et al., 1996). There were 156 analyzable patients, 36% of whom had recurrent primary brain tumors (median prior dose = 60 Gy) and 64% of whom had recurrent brain metastases (median prior dose = 30 Gy), lesions that were all less than or equal to 40 mm in maximum diameter. Initially, patients were entered into arms of the study based on the maximum diameter of their recurrent lesion: tumors of 20 mm

or less received 18 Gy; tumors ranging from 21 to 30 mm received 15 Gy; and those ranging from 31 to 40 mm received 12 Gy. Dose escalation was later carried out such that tumors smaller than 20 mm received 21 Gy; tumors between 21 and 30 mm received 18 Gy; and those between 31 and 40 mm received 15 Gy. Unacceptable acute toxicity secondary to cerebral edema was observed in 0%, 7%, and 5% of patients, respectively, in the first group. In the second, dose escalation, group, no unacceptable acute toxicity was seen. Multivariate analysis showed that maximum tumor diameter was one variable associated with significantly increased risk to patients with grade 3, 4, or 5 neurotoxicity. Specifically, patients with tumors of 21 to 40 mm in diameter were 7 to 16 times more likely to develop grade 3 to 5 neurotoxicity than those who had tumors less than 20 mm in diameter. Radiosurgery dose to the tumor was also associated with neurotoxicity. The actuarial incidence of radionecrosis was 5%, 8%, 9%, and 11% at 6, 12, 18, and 24 months after radiosurgery, respectively (Shaw et al., 1996, 2000). These results should be used as guidelines for dose selection to minimize unacceptable toxicities from radiosurgery.

Of note, in the final report of this study, a comparison between linear-accelerator-based radiosurgery and gamma knife radiosurgery results was made. The results, while interesting, cannot be meaningfully interpreted because of differences in the characteristics of the two groups of patients and the fact that this study was not originally designed to compare radiosurgical treatment units (Buatti et al., 2000).

The largest published series on external beam re-irradiation of brain metastases included 86 patients from the Mayo Clinic (Wong et al., 1996). The first course of radiation that was employed provided a median dose of 30 Gy, followed by 20 Gy for re-treatment. Patient median survival time after re-irradiation was 4 months; 27% of patients showed total symptom resolution; 43% experienced partial resolution; and 29% showed no change or had worsening of neurologic symptoms. There was no significant toxicity related to re-irradiation in the majority of patients. The only factor associated with improved survival on multivariate analysis was the absence of extracranial disease.

Another series, from New York University, included 52 patients selected for re-irradiation of recurrent cerebral metastases who were in relatively good medical condition, had an interval of at least 4 months

from the initial course of radiation, and were experiencing a renewed deterioration in neurologic condition. Patients had initially been prescribed a dose of 30 Gy in 10 fractions over 2 weeks, whereas re-irradiation consisted of 25 Gy in 10 fractions. There was a 42% response rate to re-irradiation, and survival after the second treatment averaged 5 months (Cooper et al., 1990). If eligible, patients with recurrent brain metastases should be offered radiosurgery as the treatment of choice. If radiosurgery is not feasible, then whole brain re-irradiation may be carefully considered for patients who are highly motivated and have selection criteria of age, KPS status, absence of extracranial disease, and time interval between treatments in their favor.

Prophylactic cranial radiation therapy (PCI) should be considered for patients with limited-stage small cell lung cancer in complete remission because there is a 20% to 25% incidence of developing brain metastases subsequent to initial diagnosis (Ihde et al., 1997). Debate over PCI relates to concern that the treatment may itself directly cause neurologic deficits. The endpoints to be measured are quality of life and survival. The Prophylactic Cranial Irradiation Overview Collaboration Group published a meta-analysis of 987 patients with small cell lung cancer in complete remission based on seven trials that randomized patients to receive PCI or no PCI (Auperin et al., 1999). The relative risk of death in the treatment group compared with the control groups was 0.84, corresponding to a 5.4% increase in the rate of survival at 3 years—from 15.3% in the control group to 20.7% in the treatment group. Prophylactic cranial irradiation decreased the cumulative incidence of brain metastasis with a relative risk of 0.46 ($p < 0.001$). Addressing the concern of neurocognitive impairment in patients who have undergone PCI, the investigators of the two largest trials included in the meta-analysis performed neuropsychological testing on most patients before and after treatment. Neurocognitive impairment was often detected at diagnosis, but no deterioration was found after PCI (Ariagada et al., 1995; Gregor et al., 1997). The meta-analysis makes a strong case that PCI should be included as standard care for all patients with small cell lung cancer in complete remission. Prophylactic cranial irradiation should not be given concurrently with chemotherapy, to avoid increased neurotoxicity.

The acute side effects of WBRT can include mild fatigue, reversible hair loss, and mild scalp erythema as well as hyperpigmentation. Of greater concern is

the development of somnolence syndrome, described as persistent fatigue, anorexia, and irritability (especially in children), which may occur 3 to 10 weeks after treatment but may resolve within 6 weeks (Littman et al., 1984). Long-term survivors may be at risk of developing the late effects of WBRT. Progressive dementia, ataxia, and urinary incontinence were reported 5 to 36 months after WBRT in a series of 12 patients (DeAngelis et al., 1989a). Correlative CT findings identified cortical atrophy and hypodense white matter changes in these patients. Analysis of this study reveals that large radiation fractions (3 to 6 Gy) may have contributed to an increased incidence of late toxicities associated with WBRT. Based on this report, smaller fraction sizes of 1.8 to 2.5 Gy should be considered for patients who are expected to live longer than average because of favorable prognostic factors.

In conclusion, the effectiveness of WBRT in palliating brain metastases has been established by multiple RTOG trials. Prognostic factors identified by the RTOG that predict a greater life expectancy should be used to select patients for more aggressive treatments than WBRT alone, such as radiosurgery and surgery. This is important because control of neurologic disease is likely to impact overall survival. Also, long-term survivors are at increased risk of realizing the sequelae of radiation therapy, so that a patient belonging to the most favorable risk group should be given a more protracted course of radiation using smaller fraction sizes. Additional randomized trials that address quality of life in addition to traditional endpoints will be necessary to further evaluate the respective roles of radiosurgery and surgery and to determine the best way to combine these therapies with WBRT to maximize neurologic survival and quality of life. We hope that the data presented will help the reader make evidence-based decisions in the complex management of brain metastasis, the most common tumor type afflicting the brain.

Surgery

Although radiation therapy is frequently employed in the treatment of brain metastases, surgical removal of the tumor mass, whether single or multiple, may be the most effective palliation, especially for tumors from radioresistant diseases such as melanoma and carcinomas of the kidney and colon (Galicich and Arbit, 1990; Lang and Sawaya, 1996; Lang and Sawaya, 1998; Sawaya et al., 2000). Modern neurosurgical techniques and perioperative care have changed sur-

geons' perception of surgery for brain metastases over the past 30 years. With the potential for increased benefit that surgical resection offers, this treatment has become a routine consideration for certain patients.

Series examining heterogeneous groups of patients have revealed median survival times extending from 10 to 14 months for patients treated surgically for a single metastasis (Decker et al., 1984; Sundaresan and Galicich, 1985b; Ferrara et al., 1990; Patchell et al., 1990; Bindal et al., 1993). Previously, surgery for multiple metastases had not been considered as an option (Young and Patchell, 1990; Patchell, 1991), but one study of patients treated surgically for multiple metastases showed that the median survival extended to 10 months (Bindal et al., 1993). Because resection eliminates the neoplasm and the source of brain edema, surgery should be considered for large, symptomatic tumors, whereas removal of smaller asymptomatic lesions may be delayed until they become symptomatic or show rapid growth that would predict the onset of symptoms.

Numerous retrospective studies have confirmed that surgery with WBRT is more effective than WBRT alone. With the combined treatment, recurrence at the original site of metastasis occurs significantly less frequently and functional independence is significantly longer. Reports show that for patients with no other detectable evidence of disease at the time of craniotomy, the median survival after surgery is significantly increased (Galicich et al., 1980b). In a study of 33 patients who underwent surgical resection and postoperative WBRT for solitary brain metastases, Galicich and co-workers (1980a) found a low incidence of recurrence, a median survival time of 8 months, and a 1 year survival rate of 44%. A larger study of 78 patients conducted by the same group showed a median survival of 6 months, with a 1 year survival rate of 29% (Galicich et al., 1980b).

In two other studies, patients with cancer and a single brain metastasis were prospectively randomized to receive either surgery followed by WBRT or WBRT alone (Patchell et al., 1990; Vecht et al., 1993). In the study by Patchell and co-workers, the group undergoing surgery had fewer instances of recurrence (20% versus 52%, respectively), a significantly longer median survival (40 versus 15 weeks, respectively), and longer functional independence (38 versus 8 weeks, respectively). Similarly, Vecht's group demonstrated that surgery plus WBRT was superior to WBRT alone for the treatment of patients with sin-

gle brain metastases (Vecht et al., 1993). More recently, Patchell and co-workers (1998) revealed that patients undergoing complete surgical resection of single brain metastases who also receive postoperative radiotherapy are subject to fewer tumor recurrences in the brain and die less frequently of neurologic causes than similar patients not receiving such radiotherapy; however, survival was not extended for patients receiving radiotherapy in addition to surgery.

Surgery is also beneficial for (1) controlling neurologic symptoms for patients with a functional status that dictates further treatment, (2) confirming a diagnosis that is questionable, (3) providing immediate palliation, (4) offering increased tolerance to and physician flexibility in using alternative treatments, (5) providing more durable local control, and (6) confirming or ascertaining the presence of metastases.

Patchell and co-workers (1990) noted that 6 of 54 patients initially considered to have brain metastases based on results from CT or MRI scans were found at surgery (or biopsy) to have other lesions, and 3 had no neoplastic disorder at all. These errors cannot always be precluded by diagnostic imaging and can be detected only by microscopic examination of tissue (Patchell et al., 1990).

Surgical considerations are based mainly on accessibility and resectability. Accessibility has been defined as "the risk and extent of neurologic injury the patient is willing to accept" (Moser and Johnson, 1989). The location of the lesion affects potential postoperative complications: lesions located in or near the motor cortex and Broca's speech area require particular care to avoid paresis or dysphasia; lesions located in the visual cortex can produce temporary or permanent visual deficits. For some of these lesions, techniques such as cortical mapping can be useful in minimizing damage to motor, sensory, and speech areas (Landy and Egnor, 1991), but careful pre- and intraoperative localization is vital, and each lesion must be considered individually. Lesions located deep within the brain parenchyma have traditionally been considered unresectable, but modern techniques, mainly intraoperative ultrasonography and stereotactic approaches, now allow access to these lesions (Kelly et al., 1988; Lange et al., 1990).

A factor that plays a significant role in considering resectability is the number of metastases. As late as 1990, most neuro-oncologists and neurosurgeons considered surgery for multiple metastases justified in only rare instances. The consensus was that the

presence of multiple lesions strongly contraindicated surgery and that the circumstances precipitating the rare decisions to operate on patients with multiple metastases were limited to (1) a life-threatening mass effect on the brain stem (associated with an asymptomatic or relatively radiosensitive supratentorial lesion); (2) a large, life-threatening radiosensitive supratentorial lesion; or (3) two or more lesions that could be removed through a single cranial opening (Young and Patchell, 1990). Modern technology, however, is expanding surgical options.

At M. D. Anderson, we evaluated the results of surgery in patients with multiple lesions and found that surgery can play a very important role in managing these patients (Bindal et al., 1993). Fifty-six patients who underwent surgery for multiple brain metastases were divided into two groups: group A, those patients who had one or more lesions remaining after surgery ($N = 30$); and group B, those patients who had all lesions removed ($N = 26$). Patients in group B were matched by type of primary tumor, presence or absence of systemic disease, and time from first diagnosis of cancer to diagnosis of brain metastases to a third group of patients (group C, $N = 26$), undergoing surgery for a single lesion. Median survival times were 6, 14, and 14 months for patients in groups A, B, and C, respectively. Besides the significant difference in survival between groups A and B ($p = 0.003$) and between groups A and C ($p = 0.012$) there was a significant correspondence in recurrence or neurologic improvement rates between groups B and C, indicating that surgery for patients with multiple metastatic lesions that can all be removed is as effective as surgery for a single lesion. Although the results appear intuitively correct, a larger study may be required to confirm and expand these findings.

Patients with multiple brain metastases in whom all lesions cannot be surgically excised may also be candidates for surgery if resection of one or more highly symptomatic, debilitating, or life-threatening lesions will result in greater, more rapid palliation of symptoms than might be achieved by irradiation alone.

Although the microsurgical techniques used for the removal of brain metastases are largely the same as those used for the removal of other intracranial lesions, surgery is complicated by the generally small size of the tumors and the tendency of a cerebral metastasis to cause extensive edema with resulting neurologic symptoms, a factor that accounts for early di-

agnosis but contributes to the difficulty in locating metastases if they are not superficial. Modern imaging techniques allow for more efficacious treatment of asymptomatic tumors that may be discovered at the time that systemic cancers are first diagnosed and that, consequently, may still be quite small. Computer-assisted stereotactic and/or intraoperative ultrasound techniques (1) allow surgeons to precisely locate the tumor before making the cortical incision; (2) provide a direct route to the tumor that avoids eloquent areas of the brain; (3) aid surgeons in placing the bone flap precisely over the tumor location; and (4) eliminate the need to extensively probe for an elusive tumor, which can result in neurologic damage.

For patients experiencing considerable mass effect from the tumor, repeated preoperative CT scans help monitor the edema, which can be reduced in most cases by administering steroids. The preoperative administration of corticosteroids for a minimum of 48 hours helps prevent transdural herniation when the tumor is exposed. Administration of diuretics should be undertaken with caution because they reduce the extracellular volume and induce hyponatremia and vasoconstriction. Effective control of edema during surgery can be achieved by using a proper, safe anesthesiologic procedure (Gambardella et al., 1990). Surgery is limited by the functional importance of the brain tissue to be traversed. Another major consideration is the expected quality of survival, a subjectively determined factor. For one patient, a few months of restored neurologic function might be very important, whereas it might be of minimal significance for another patient.

Surgery and imaging technology came together in 1986 in the first successful removal of a lesion metastatic to the tectum of the midbrain (Tobler et al., 1986). Although metastasis to this site is a very rare occurrence (1% to 3% of brain metastases) and was previously considered an inoperable location, the tumor was vaporized with a carbon dioxide laser beam (up to 20 watts) and removed by a central coring technique. For patients with systemic cancer that cannot be controlled, management decisions for asymptomatic brain tumors are moot.

As noted previously, early neurosurgical attempts met with high rates of complications due to unsophisticated radiographic methods and a limited ability to control brain herniation. Modern advances, including the use of corticosteroids and modern anesthesia, the advent of CT and MRI, the use of the

surgical microscope, and the development of intraoperative ultrasound, stereotactic localization, and cortical mapping, have significantly reduced operative mortalities and morbidities (Sawaya et al., 1998). Postoperative mortality is most often due to uncontrolled systemic cancer, but comparisons of results from gross total removal and partial removal of brain metastases indicate that the former yields the lowest rate of operative mortality and that the 30 day mortality risk may be doubled in cases of partial removal (Haar and Patterson, 1972). A recent study of neurosurgical outcomes in a series of 400 craniotomies performed for removal of brain metastases (48%) or gliomas (52%) (Sawaya et al., 1998) determined that gross total resection of most tumors (73%) did not lead to more major neurologic deficits than were observed for patients undergoing subtotal or partial resection. Nonfatal complications such as hematomas, wound infections, and pseudomeningocele formations, which occur in 8% to 9% of all craniotomies for brain metastases (Bindal et al., 1993), as well as surgically induced neurologic impairments, are usually transient events. Clinically evident thromboembolic complications, such as deep vein thrombosis or pulmonary embolism, occur in an estimated 10% of patients (Constantini et al., 1991; Sawaya et al., 1992). Mortality and morbidity rates have been reduced to 3% or less and 5% or less, respectively (Sundaresan and Galicich, 1985a; Brega et al., 1990; Patchell et al., 1990; Bindal et al., 1993).

Chemotherapy

Systemic chemotherapy has historically been considered ineffective in the treatment of brain metastases, with several reasons being given for this presumed failure (Buckner, 1991). The BBB has been assumed to be a major restriction to the CNS entry of many cytotoxic drugs that are large polar or hydrophobic compounds. Unlike normal brain capillaries, tumor capillaries are variably disrupted in patients who have brain metastases (and high-grade primary brain tumors). Evidence that the tumor capillaries in most metastatic tumors are disrupted is shown by the fact that virtually all metastatic tumors in the brain are contrast enhancing, reflecting the leakage of contrast material from the tumor vasculature to the interstitium. Drugs (cisplatin, etoposide, nimustine, and aziquinone) administered before surgery and measured

in tumor samples removed at surgery have consistently demonstrated pharmacologically relevant levels in these tissues, suggesting that these agents are able to penetrate the tumor tissue in the brain when delivered systemically (Stewart et al., 1979; Stewart et al., 1982; Savaraj et al., 1983, 1984). Most animal studies, however, have shown lower capillary permeability and lower drug concentrations in brain tumors than in subcutaneous tumors for systemically administered chemotherapy (Stewart, 1994).

Lipophilic drugs such as nitrosoureas or other semisynthetic agents may be able to deliver even higher levels of drugs to the tumor periphery where the BBB may remain relatively intact (Levin et al., 1975, 1976). Some drugs may, however, inadequately penetrate tumor regions and will achieve subtherapeutic levels intracellularly (Levin et al., 1980). The observation of CNS relapse before relapse at other sites in acute leukemia and small cell lung cancer is often cited as evidence of the importance of the BBB in inhibiting the effectiveness of chemotherapy. Blood-brain barrier disruption with hyperosmolar agents, to increase chemotherapy delivery to brain, has been developed for primary brain tumors but has not yet been investigated for brain metastasis treatment.

The routine use of corticosteroids, which are capable of re-establishing disrupted BBB function, for symptomatic brain metastasis may provide an additional protective effect against cytotoxic agents (Weller et al., 1997; Mariotta et al., 1999) and may further limit drug delivery into CNS tumors (Nakagawa et al., 1987).

Cancers that most frequently metastasize to the brain, such as non-small cell lung cancer and malignant melanoma, are often inherently insensitive to systemic chemotherapy. Many patients develop brain metastases in the face of widespread systemic relapse and/or after failure of several prior treatment regimens, including radiotherapy and chemotherapy. While long-duration chemotherapy treatment can increase the frequency of acquired resistance to chemotherapy agents for brain tumor metastases because of increased expression of efflux pumps such as the P-glycoprotein, encoded by the multidrug-resistance-1 gene, nonetheless, the intact BBB already has functioning efflux pumps such as the P-glycoprotein, raising the question whether this is truly an acquired mechanism or a common *de novo* mechanism for drug failure of tumors in the brain.

Several lines of evidence suggest that a number of different chemotherapy regimens may be at least palliative with respect to some brain metastases (Greig, 1984). An increasing number of clinical trials have demonstrated response rates for brain metastases that are in keeping with those seen for systemic metastases using the same regimens, especially for breast and lung carcinomas.

Several clinical trials have reported the activity of single-agent and combination chemotherapy in some types of brain metastases. Breast carcinomas, in general, are considered chemosensitive tumors. Patients with extracranial metastatic breast carcinomas who have not had prior chemotherapy can achieve 50% to 70% response rates with combination chemotherapy, but only 20% to 30% of patients who failed prior chemotherapy will respond to second-line salvage chemotherapy. Rosner and coworkers (1986) demonstrated a response rate of >50% using cyclophosphamide, 5-fluorouracil, and prednisone in 100 breast cancer patients with cerebral metastasis. The best result reported to date has been with a five-drug combination—cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone (CM-FVP) with which Rosner and colleagues (1986) found 10% complete and 40% partial response rates for patients not receiving prior chemotherapy. There were some long-term survivors, but the median duration of response was only 7 months, and survival was similarly quite short. Several points should be emphasized in this study: (1) patients with brain metastases responded to combination chemotherapy at a rate similar to that experienced by patients treated for extracranial metastases; (2) patients who failed initial chemotherapy did respond, albeit at a lower rate, to second- or third-line regimens; (3) all patients received prednisone, an antiedema agent that may interfere with the response interpretation because of a prednisone-mediated decrease in edema and mass effect as visualized on neuroimaging studies; and (4) the high response rates have not been reproduced by other investigators (Flowers and Levin, 1993).

Other drug regimens, including etoposide and cisplatin (Cocconi et al., 1990; Franciosi et al., 1999) and CAF (cyclophosphamide, doxorubicin, and fluorouracil) have shown similar activities for breast carcinoma brain metastases with response rates in the range of 40% to 50%. A multidrug combination called TPDC-FuHu (6-thioguanine, procarbazine, dibromodulcitol, lomustine, fluorouracil, and hydrox-

yurea) that focused on overcoming nitrosourea resistance and potentiating nitrosourea tumor cell kill demonstrated similar results for patients with brain metastases from breast and non-small cell lung carcinoma and considerably better results for patients with small cell lung carcinoma who failed prior radiation therapy for these metastases. For patients with brain metastases from breast, non-small cell and small cell lung carcinoma, response rates were 36%, 26%, and 67%, respectively. The corresponding disease-free survival periods for these responding patient subgroups were 27, 21, and 133 weeks, respectively (Kaba et al., 1997).

Among the various lung cancers, small cell carcinoma is the most sensitive to chemotherapy. Lee and co-workers (1989) reported the use of cyclophosphamide, doxorubicin, vincristine, and etoposide as primary chemotherapy for 15 patients with small cell lung cancer who presented with brain metastases. Nine of 11 evaluable patients (82%) showed complete or partial responses. In another study, Twelves and co-workers (1990) treated 14 patients who had brain metastases from small cell lung cancer at presentation with cyclophosphamide, vincristine, and etoposide. Nine patients (64%) responded. In contrast, results from small studies in which chemotherapy combinations with etoposide and cisplatin (Croisile et al., 1992), fotemustine plus cisplatin (Cotto et al., 1996), and lomustine, carboplatin, vinorelbine, and fluorouracil (Colleoni et al., 1997) were used to treat brain metastases from non-small cell lung carcinoma (a less chemosensitive tumor type) were much less impressive. Response rates for patients in these studies were 0%, 14%, and 33%, respectively, to chemotherapy. Robinet and colleagues (1991) reported a 50% response rate using fluorouracil and cisplatin; however, this result has not yet been duplicated. These results suggest that the response of cerebral metastases to chemotherapy may depend on the inherent chemosensitivity of the primary cancer type.

Historically, malignant melanoma has been shown to be extremely insensitive to chemotherapy, with brain metastases from melanoma being no exception. However, a meeting abstract in 1996 reported that use of cisplatin combined with interleukin-2 and interferon- α_{2a} to treat brain metastases from melanoma had shown improved results with a response rate of 39% and a median survival time of 32 weeks (Mousseau et al., 1996).

Several studies of brain metastases from other systemic chemosensitive cancers, such as choriocarcinoma and germinoma, have demonstrated high response rates to combination chemotherapy regimens that are deemed active for the systemic cancers. In one study, 13 of 18 (72%) patients with choriocarcinoma and brain metastasis responded to primary chemotherapy with etoposide, methotrexate, dactinomycin, vincristine, cyclophosphamide, and cisplatin (Rustin et al., 1989), whereas in another study, 8 of 10 patients (80%) diagnosed with germinoma and brain metastases achieved complete response to cisplatin, vincristine, methotrexate, bleomycin, etoposide, dactinomycin, and cyclophosphamide (Rustin et al., 1986). In gestational trophoblastic disease metastatic to the brain, combination chemotherapy with etoposide, methotrexate, vincristine, actinomycin-D, and cyclophosphamide as sole therapy can be curative.

The role of chemotherapy in the overall management of patients with brain metastases remains under investigation. Chemotherapy should be considered for chemosensitive tumors, keeping in mind that surgery and radiotherapy remain the primary treatment modalities. There is insufficient positive experience to support the general use of chemotherapy in patients with brain metastases; therefore, chemotherapy should be considered as palliative and should be given under the auspices of appropriately designed clinical trials. The choice of the drug or drug combination should be guided by the chemosensitivity profile of the primary systemic cancer. Future treatment approaches may involve pre-radiation chemotherapy for patients who have minimal neurologic symptoms, which may reduce the tumor burden in the brain, allowing more prolonged control after radiation therapy and, perhaps, decreased radiation neurotoxicity, if the radiation dose can be reduced.

The role of the BBB in restricting drug entry into brain regions adjacent to a tumor probably plays some role in the efficacy of chemotherapy for brain metastases. The use of corticosteroids by these patients should be carefully limited as much as possible to allow maximal benefit from chemotherapeutic agents while maintaining neurologic function. Adjustments in steroid dose must be taken into consideration in clinical trial design, as the dose and the timing of steroid administration may partially rectify a leaky tumor vasculature and falsely produce a response on CT or MRI scans.

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